In response to the Restriction Requirement of March 12, 2002, the applicants elected the species of Claim 30. The Office has used the elected species to restrict the invention into two groups, Group I drawn to compounds, compositions, and methods wherein R_1 and R_2 represent everything but heteroaryls defined in the claims; and Group II is drawn to those compounds, compositions, and methods wherein R_1 and R_2 are those heteroaryls. Based on the elected species, the applicants are assumed to have elected the invention of Group I. The Office has withdrawn the non-elected subject matter from consideration and the applicants hereby amend the claims to conform with the election.

The remainder of the Office Action pertains to rejections under 35 USC § 112. To begin with, the broad compound claims are rejected under 35 USC § 112, first paragraph, for lack of enablement. Specifically, the Office questions the enablement of the R_1 and R_2 nitrogen containing heterocycles, and the heteroaryl rings possible at A. The applicants assume that the rejection based on the scope of the R_1 and R_2 nitrogen containing heterocycles is moot based on the election of Restriction Group I. With regard to the rejection for the definition of the heteroaryl groups at A, the applicants have, with this Response and Amendment, amended the definition of the heteroaryl group to specify specific moieties.

The Office then rejects broad method Claim 31 under 35 USC § 112, first paragraph, for indefiniteness because the Office considers it impossible to clearly define the scope of the claim to nicotinic ligands of α_4-ß$_2$ receptors. Similarly, Method Claim 32 is rejected for lack of enablement because the Office does not find the Specification to provide enablement for the numerous conditions claimed to be treatable.

With this Response and Amendment, the applicants provide a Declaration and literature review by a scientist skilled in this particular art which speaks to the objections of the Office. Specifically, the Declarant provides empirical evidence that representative compounds of the instant invention possess binding activity which one skilled in the art would find enabling of the claimed therapeutic activity. Representative compounds are shown in Table 1 of the Declaration to actively bind *in vitro* at central α_4-ß$_2$ nicotinic receptors in excised rat brains according to the assay presented at Example 42. Representative compounds are shown in Table 2 to increase the *in vivo* release of acetylcholine in rat brains under the protocol of Example 43, thereby demonstrating dose-dependent α_4-ß$_2$ nicotinic receptor agonist character. In the analgesic model of Example 44, representative compounds of the instant invention are shown to antagonize phenyl-p-benzoquinone (PBQ) induced abdominal contractions in mice in a dose-dependent manner, demonstrating *in vivo* antalgic activity. Finally, the Declarant presents *in vivo* social recognition data in rats for representative compounds of the instant invention in Table 4. Representative compounds are shown in a dose-dependent manner to significantly enhance social memorization under the protocol of Example 45. Thus, the applicants have supplied enabling disclosure of the claimed α_4-ß$_2$ nicotinic receptor activity, which activity is directly correlated with therapeutic efficacy according to the following paragraph.

Following-up on the enabling *in-vitro* and *in vivo* pharmacological demonstration, the Declarant provides a literature review correlating the demonstrated pharmacological activity of the instant compounds with treating a well defined group of conditions, which conditions include age-related cognitive disorders and Alzheimer's disease, dementia, Schizophrenia, attention-deficit/hyperactivity disorder, depression, Tourette's syndrome, neurodegeneration and anxiety;

providing analgesia; and assisting in smoking cessation. It is submitted that one skilled in the art would understand that compounds demonstrated to be α_4-ß$_2$ nicotinic receptor (central receptor) ligands will be effective in treating a well defined subset of conditions. The applicants have provided a literature review of the conditions which are acknowledged by those skilled in the art to be treatable with such compounds. Thus, it is submitted that the scope of conditions treatable by α_4-ß$_2$ nicotinic receptor (central receptor) ligands is a defined group of conditions. Reconsideration and withdrawal of the enablement and indefiniteness rejections is respectfully solicited.

Finally, Claims 34-36 are rejected under 35 USC § 112, second paragraph for failing to claim with particularity because US Patent Office procedure does not accept "useful for" language in pharmaceutical composition claims. With this Response and Amendment, the applicants have consolidated the Pharmaceutical Composition claims into one claim which does not include any "use" language. The applicants believe that this amendment is responsive to the Office's objections.

* * * * *

Accordingly, entry of the present Declaration and amendment, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

By: _____
G. PATRICK SAGE

Dated: December 18, 2002
Customer No.: 25,666
500 Columbia Plaza
350 East Michigan Ave.
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(616) 382-0030

Enclosure: Three (3) month extension fee,

Amended Claims in Clean and Marked-up form,

Declaration under 37 CFR § 1.132, Form PTO-1449 and accompanying references, and

Postal Card Receipt.

* * * * *

THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR DEFECT IN THE ATTACHED CHECK, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.

CLAIMS (MARKED-UP)

19 A compound selected from those of formula (I) :

(I),

wherein :

p represents an integer of from 0 to 6 inclusive,

n represents an integer of from 0 to 6 inclusive,

R_1 and R_2, which may be identical or different, each independently of the other represent a group selected from hydrogen, linear or branched (C_1-C_6)alkyl, aryl, and aryl-(C_1-C_6)alkyl in which alkyl is linear or branched, [or R_1+R_2 form together with the nitrogen carrying them saturated, a 3- to 10-membered, monocyclic, or bicyclic system, optionally containing a second hetero atom selected from oxygen, nitrogen, and sulphur,]

X represents a group selected from oxygen, sulphur, -CH=CH-, methylene, a group of formula -HC=N-O- and a group of formula -O-CH_2-CH=CH-, in which groups oxygen is linked to Y of formula (I),

Y represents a group selected from aryl, heteroaryl, aryl-(C_1-C_6)alkyl in which the alkyl moiety is linear or branched, heteroaryl-(C_1-C_6)alkyl in which alkyl is linear or branched, -C(O)-A, and -C(S)-A,

A represents a group selected from linear or branched (C_1-C_6)alkyl, aryl, heteroaryl, aryl-(C_1-C_6)alkyl in which alkyl is linear or branched, heteroaryl-(C_1-C_6)alkyl in which alkyl is linear or branched, and NR_3R_4 wherein R_3, and R_4, which may be identical or different, each represent a group selected from hydrogen, linear or branched (C_1-C_6)alkyl, aryl, and aryl-(C_1-C_6)alkyl in which alkyl is linear or branched, or R_3+R_4 form together with nitrogen carrying them a monocyclic, or bicyclic (C_3-C_{10}) system,

its isomers and addition salts thereof with a pharmaceutically-acceptable acid or base,

with the proviso that :

♦ *in the case of 1,1-disubstituted compounds of formula (I),*

- p is other than zero, when X represents methylene, n has the value zero, Y represents aryl, or heteroaryl, and R_1, and R_2, which may be identical or different, represent hydrogen, linear or branched (C_1-C_4)alkyl, benzyl, phenylethyl, or form together with the nitrogen carrying them morpholino, thiomorpholino, or a 5- to 7-membered saturated carbocyclic system,
- p is other than zero, when X represents methylene, n has the value zero, Y represents acetyl, and R_1, and R_2, which may be identical or different, represent hydrogen, linear or branched (C_1-C_4)alkyl, phenyl, benzyl, or form together with the nitrogen carrying them piperidyl, or morpholino,
- R_1, and R_2 do not simultaneously represent methyl:
  * either, when p, and n each have the value 1, X represents oxygen, and Y is selected from p-nitrobenzoyl, p-aminobenzoyl, p-chlorophenylaminocarbonyl, and acetyl,
  * or, when p has the value zero, n has the value 1, X represents oxygen, or sulphur, and Y represents 2-quinolyl substituted in the 3-position by linear or branched (C_3-C_4)alkyl, or phenyl,
- Y does not represent 1,2-benzisoxazol-3-yl when n has the value 1, p has the value zero, and X represents oxygen,

♦ *in the case of 1,2-disubstituted compounds of formula (I),*

- R_1, and R_2 do not simultaneously represent hydrogen when p, and n each have the value zero, and X-Y together represent phenoxy (optionally substituted by one or two, identical or different, groups selected from methoxy, dimethylamino, halogen, methyl, trifluoromethyl, nitro, and amino), phenylsulphanyl, benzyloxy, benzyl, or 2-phenylethyl,
- R_1 and R_2 do not simultaneously represent methyl when p, and n each have the value zero and X-Y together represent phenoxy (optionally substituted by a group selected from chlorine, and trifluoromethyl), phenylsulphanyl, or benzyl,

and also with the proviso that the compounds of formula (I) are other than the following

compounds :

- (1-benzylcyclopropyl)methanamine,
- (1-benzylcyclopropyl)-N,N-dimethylmethanamine,
- 2-(phenoxycyclopropyl)methanamine,
- 2-(phenoxymethyl)-cyclopropanamine,
- (N,N-dimethyl)-2-(acetoxymethyl)-cyclopropanemethanamine,
- N-{2-[2-(benzyloxy)ethyl]cyclopropyl}-N,N-dimethylamine.

it also being understood that :

- aryl denotes phenyl, biphenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indanyl, or indenyl, each of those groups being optionally substituted by one or more, identical or different, groups selected from halogen, linear or branched (C_1-C_6)alkyl, hydroxy, cyano, nitro, linear or branched (C_1-C_6)alkoxy, linear or branched (C_2-C_7)acyl, linear or branched (C_1-C_6)alkoxycarbonyl, linear or branched (C_1-C_6)trihaloalkyl, linear or branched (C_1-C_6)trihaloalkoxy, and amino optionally substituted by one or two linear or branched (C_1-C_6)alkyl,

- heteroaryl denotes a thienyl, pyridyl, furyl, pyrrolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl or quinolyl group, [denotes 5- to 12-membered, monocyclic aromatic or bicyclic system containing from one to three, identical or different, hetero atoms selected from oxygen, nitrogen and sulphur, one of the rings of which, in the case of bicyclic system, is aromatic in character, and the other ring of which may be aromatic, or partially hydrogenated,] each of those groups being optionally substituted by one or more, identical or different, groups selected from substituents defined hereinbefore for aryl.

34- A pharmaceutical composition [useful as specific nicotinic ligands of $\alpha_4\beta_2$ receptors,] comprising as active principle an effective amount of a compound as claimed in claim 19, alone or in combination with one or more pharmaceutically-acceptable excipients or carriers.